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08/796,040	02/05/1997	METIN COLPAN	P58126US1	8477

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EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	52

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/796,040	Applicant(s) Colpan	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--3--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on **-09/17/03** (RCE, amdt J & IDS)-.
[] This action is **FINAL.**
[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims **---120-138---** are pending in the application. Claims -**101-119-** have been cancelled.
Of the above claim(s) **---[]---** is/are withdrawn from consideration.
[] Claim(s) **---[]---** is/are allowed.
[X] Claims **---120-138---** are rejected.
[] Claim(s) **---[]---** is/are objected to.
[] Claim(s) **---[]---** are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[] The proposed drawing correction, filed on **-[]-** are [] approved [] disapproved.
[] The drawing(s) filed on **-[]-** is/are objected to by the Examiner.
[] The specification is objected to by the Examiner.
[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
[X] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) **-[]-**.
[X] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: **-[]-**.

Attachment(s)

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). **--51--**
[] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413
[] Notice of Informal Patent Application, PTO-152
[] Other: **-[]-**.

Claims **101-119** have been cancelled, no claims have been amended, the disclosure has not been amended, and new claims **120-138** have been added as per the RCE and amendment filed September 17, 2003. An Information Disclosure Statement (IDS) has been received September 17, 2003 and made of record.

Claims **120-138** remain in the case.

Claim **136** is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **136**, at line 4, the term "alcoholic solution" is indefinite because it refers to both salt containing alcoholic solutions in the first three lines of the noted claim and subsequently to alcohols and mixtures thereof at the end of the claim. Examiner respectfully requests that the noted term be amended to read -- the alcoholic portion of the alcoholic solution -- in order to clarify the intended meaning of the claim and remove any remaining indefiniteness.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **120-138** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Henco et al. '426** (PTO-892 ref. **I**) in view of **Little '430** (PTO-1449 ref. **AC**), and further in view of the International Dictionary of Medicine and Biology (PTO-892 ref. **S**) and **Hames et al.** (PTO-892 ref. **R**).

The instant claims are directed to a process for DNA purification with the following steps:
i) cell lysis using an enzyme (e.g. RNase A) or using a mixture of chemical reagents (e.g. buffered SDS) and debris removal using filtration and/or centrifugation;
ii) contacting the filtrate from step i) with an anion exchange resin in buffers of low ionic strength, and elution of the DNA from the anion exchange resin by contacting with a high-ionic-strength buffer, optionally following the addition of a lower alcohol, or of polyethylene glycol, and
iv) desalting the DNA-containing solution by contacting same with a mineral support material to effect adsorption of the DNA onto the mineral support material (e.g silica gel) followed by washing the adsorbed DNA with alcoholic solutions to remove salts, and elution of DNA from the mineral adsorbent by contacting the mineral support material with a low ionic strength buffer (e.g. buffered Tris) or with water.

Henco et al. '426 discloses a four step process summarized as follows:
i) cell lysis/filtration by any one of numerous known methods including the use of detergents, proteolytic enzymes or mechanical procedures (see claim 8) including centrifugation (see column 6, lines 51-66);
ii) anion exchange chromatography by transferring the product solution

from step i) to an anion exchange resin followed by washing with a low ionic strength buffer the intended effect of which is to remove all of the interfering substances (e.g. RNA, proteins) from long chain DNA which remains adsorbed on the column optionally in the presence of known DNA precipitants polyethylene glycol or isopropanol (see col. 12, lines 41-42);
iii) elution of the long chain DNA from the anion exchange column adsorbent with high ionic strength buffer; and
iv) desalting the DNA by one of several different methods. One method of desalting not mentioned in the Henco disclosure is adsorption chromatography wherein a sample of DNA is applied to the column adsorbent such as silica gel in the presence of a high ionic strength buffer and separated therefrom by subsequent elution with low ionic strength buffer or water alone.

Little '430 at column 7, lines 12-45, discloses one of several examples wherein DNA is extracted from cells of various types using chaotropic ion/enzyme-mediated digestion followed by centrifugation and ultimately chromatographic separation using a commercial diatomaceous earth (Celite™) and various buffer solutions. As noted in the abstract, Little discloses the application of DNA to the adsorbent from a relative high ionic strength solution, washing to remove salts, and subsequent elution of the adsorbed DNA with a low ionic strength buffer or with water. This reference does not disclose the use of anion exchange resins to selectively retain DNA in a purification process.

To make clear the meaning of the **Henco et al. '426** disclosure two additional definitional references have been cited along with the relevant portion of Henco to provide a more complete basis for the instant rejection. The term "chaotropic" is defined in International Dictionary of Medicine and Biology, Vol. 1, at p. 522 to be a word

describing an agent which " ... destroys the the order of water when dissolved in it and thereby raises the solubility of hydrophilic substances in the solution." Further definitional exemplification is provided by **Hames et al.** (Nucleic Acid Hybridisation - A Practical Approach) via the indexing of "Chaotropic agents" at p. 235, which refers to pages 64-65 wherein a list of compounds is provided at p. 65, lines 10-12 and includes i) ethylene glycol, ii) sodium perchlorate, iii) tetramethylammonium chloride, iv) tetraethylammonium chloride and v) urea. (emphais added) The Henco reference does not make any generic reference to "chaotropic agents," but at column 8, line 61 Henco specifies "urea" as a component of the viral lysis mixture.

Applicant's combination of,
a) conventional cell lysis,
b) the physical separation of cell debris,
c) the anionic exchange chromatography of the filtrate isolated from the cell debris, and
d) finally desalting of the DNA-containing eluate form the anion exchange column by application to a chromatographic adsorbent (e.g. silica gel) to effect the desalting,

is a combination of process steps well known in the prior art and motivated generically by the disclosures of **Henco et al. '426**, with specific desalting step details disclosed by the **Little '430** reference. As noted supra, Henco does teach the use of DNA desalting subsequent to anion exchange. The failure to teach the specific desalting method of the instant claimed method by **Henco '426** has been addressed in the instant rejection of record by combining **Henco et al. '426** with the **Little '430** reference, wherein the latter reference discloses the utility of classical chromatography adsorbents for the purpose of isolating purified DNA in solutions with low net ionic strength. For this reason

applicant's claimed process has been found to be nothing more than a combination of the **Henco '426** reference with **Little et al.'430**, wherein Henco provides the motivation to combine by noting the need to desalt the high-ionic-strength solution of DNA produced by anion exchange chromatography (see column 7, lines 44-46; or col. 12, lines 42-43). The specific details of washing steps, the timing of steps, the specific selection of wash solution contents, and the physical characteristics of the anion exchange resin and mineral adsorbent (e.g., particle diameter, pore size, etc.) are deemed to be variables clearly within the purview of the ordinary practitioner seeking to optimize the Henco and Little process steps for a specific situation. Therefore, the details of adsorbent choice, or other standard performance parameters (e.g. the frequency of washes, the variation of ionic strength in wash solutions, etc.) are deemed to be the kind of variables properly within the realm of routine experimentation by an ordinary practitioner in the course of optimizing the process steps disclosed in the prior art of record. For these reasons, the instant claims, in so far as they are directed to routine changes in experimental details of the kind noted above, are deemed to lack an adequate basis for a finding of patentable distinction for any variation of the instant claimed process, as such variations are deemed to have been properly included within the scope of the noted prior art.

Therefore, the instant claimed process for DNA purification by anion exchange chromatography followed by desalting using an entirely conventional adsorption chromatographic process would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed September 17, 2003 have been fully considered but they are not deemed to be persuasive.

Applicant argues at page 7, lines 3-7, of the noted response applicant avers that the instant rejection as presented " ... does not make any sense at all." Examiner respectfully disagrees with this generic conclusion, noting that applicant did not file an appeal brief. Moreover, Examiner responds in detail to applicant's further criticisms in subsequent paragraphs.

Applicant at page 9, lines 9-22, then argues that a statement not found in the previous Office action, but in the Office action immediately preceding the Final rejection concerning the solution behavior of NaCl must be incorrect (NaCl asserted to be a chaotropic substance), but in the preamble to this conclusion notes that while Na^+ ion is water-ordering ("kosmotrope") while Cl^- ion is a water-disordering ion ("chaotrope"), but fails to both provide the literature source of the lyotropic series provided , and fails to establish the character of the compound sodium chloride (NaCl) as being either a net "kosmotropic" or a "chaotropic" substance. Therefore, applicant's assertion that examiner's proposed conclusion ("NaCl must also be a chaotropic agent") is "incorrect" is not factually based and, in the absence of an unambiguous showing to the contrary, is presumed to be unsubstantiated speculation. Examiner also notes that the ion "hydrogen phosphate" (" $HPO4^{2-}$ ") is found to occur twice in the second series suggesting that applicant is either also confused or has not carefully proof read his own arguments.

Applicant then argues an obscure point about urea and when it is used in Henco '426, but the argument is so convoluted that it is unclear how this relates to the question of patentability of the instant claims in view of the rejection of record. Clarification and/or recapitulation is

respectfully requested with careful editing to insure correction of spelling errors.

Applicant then argues that the Little '430 reference is not properly combined with the Henco '426 reference because of the absence of proper motivation. Examiner respectfully disagrees, noting that Little provides the detailed teaching of how to desalt not provided in Henco, but that Henco '426 clearly provides the motivation to combine by listing desalting as an optional step in the nucleic acid isolation process disclosed therein.

The arguments presented buy applicant at pages 16-17 include numerous typographical and/or spelling errors and are so disjointed as to be nearly unintelligible. Applicant is respectfully requested to resubmit these arguments in a more clearly drafted and edited form so a proper response may be timely provided without the need to guess what applicant's arguments are intended to mean.

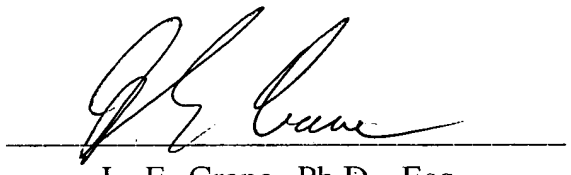
Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at (703)-308-4624.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
11/17/03



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